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Selective Catalytic Oxidation of Alcohols, Aldehydes, Alkanes and Alkenes Employing Manganese Catalysts and Hydrogen Peroxide

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Abstract: The manganese-containing catalytic system $[\text{Mn}^{\text{IV,IV}}_2\text{O}_3(\text{tmtacn})_2]^{2+}$ (**1**)/carboxylic acid (where $\text{tmtacn} = N,N',N''$ -trimethyl-1,4,7-triazacyclononane), initially identified for the *cis*-dihydroxylation and epoxidation of alkenes, is applied for a wide range of oxidative transformations, including oxidation of alkanes, alcohols and aldehydes employing H_2O_2 as oxidant. The substrate classes examined include primary and secondary aliphatic and aromatic alcohols, aldehydes, and alkenes. The emphasis is not primarily on identifying optimum conditions for each individual substrate, but understanding the various factors that affect the reactivity of the Mn-tmtacn cata-

lytic system and to explore which functional groups are oxidised preferentially. This catalytic system, of which the reactivity can be tuned by variation of the carboxylato ligands of the *in situ* formed $[\text{Mn}^{\text{III,III}}_2(\text{O})(\text{RCO}_2)_2(\text{tmtacn})_2]^{2+}$ dimers, employs H_2O_2 in a highly atom efficient manner. In addition, several substrates containing more than one oxidation sensitive group could be oxidised selectively, in certain cases even in the absence of protecting groups.

Keywords: homogeneous catalysis; manganese; oxidation; peroxides; triazacyclononane

Introduction

Oxidative transformations, in particular the oxidation of alkenes to their corresponding diols or epoxides,^[1,2] alcohols to aldehydes, ketones or carboxylic acids and oxidation of alkanes are central processes in biology, synthetic organic chemistry and industrial chemistry.^[3] In recent years, the development of atom-efficient and environmentally benign catalytic systems has been a major challenge.^[4] A primary goal is to develop systems that show high atom efficiency and minimal formation of by-products, with molecular oxygen (O_2) and hydrogen peroxide (H_2O_2) being the most atom economic oxidants.^[5,6]

Over the last two decades several groups have focused on the use of manganese catalysts based on the ligand N,N',N'' -trimethyl-1,4,7-triazacyclononane (tmtacn) originally developed by Wieghardt and co-workers in the late 1980s as model systems for the water splitting component of photosystem II (PS II) and dinuclear manganese-based catalase en-

zymes.^[7,8,9,10] The first report on the use of $[\text{Mn}^{\text{IV,IV}}_2\text{O}_3(\text{tmtacn})_2]^{2+}$ (**1**) (Figure 1) as a catalyst was by Hage et al. in 1994, where it was employed in an aqueous carbonate buffer (pH 8–9) with H_2O_2 as terminal oxidant for clean and efficient low-temperature laundry bleaching as well as the epoxidation of alkenes (albeit typically with 100 equiv. of H_2O_2 with respect to alkene).^[11] Since then, several research groups have focused on applying this catalyst in oxidative transformations with initial efforts directed towards the use of

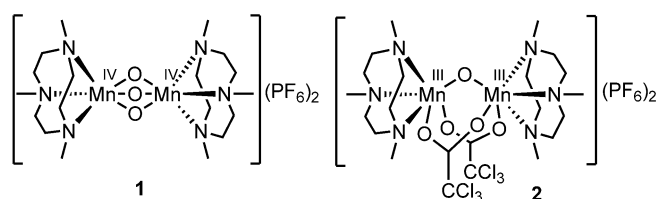


Figure 1. Complexes $[\text{Mn}^{\text{IV,IV}}_2\text{O}_3(\text{tmtacn})_2](\text{PF}_6)_2$ **1** and $[\text{Mn}^{\text{III,III}}_2\text{O}(\text{CCl}_3\text{CO}_2)_2(\text{tmtacn})_2](\text{PF}_6)_2$ **2**.

additives to suppress the catalase-type activity (i.e., wasteful decomposition of H_2O_2) of **1** and to enhance its activity towards the oxidation of alkenes.^[12,13,14,15] De Vos et al. reported the efficient epoxidation of a range of alkenes using this catalyst in oxalate-buffered aqueous acetonitrile. Under these conditions the catalase-type activity was suppressed effectively (typically 1.5–3 equiv. H_2O_2 were required).^[16] Subsequently, Berkessel and co-workers showed that a mixture of L-ascorbic acid and sodium L-ascorbate in combination with tmtacn and Mn^{II} could be used in the epoxidation of alkenes and the oxidation of alcohols, albeit with excess H_2O_2 (typically 2–2.6 equiv.).^[17] The range of substrate classes that have been examined with Mn-tmtacn-based catalysts now includes alkanes, alkenes, primary and secondary alcohols and allylic alcohols.^[14,18] Later reports showed that the catalytic activity of the Mn-tmtacn system towards oxidation of alkanes and epoxidation of alkenes could be enhanced dramatically in the presence of a large excess of acid, e.g., acetic acid (typically 40 to >100 mol%),^[19] or aldehydes such as chloral (typically 25 mol%),^[20] respectively. Importantly, in the latter case, and in the earlier example by De Vos et al.^[21] with a heterogeneous version of this catalyst, Mn-catalysed *cis*-dihydroxylation was observed also. Subsequently, it was shown by our group that carboxylic acids at co-catalytic levels (typically 1 mol%) were the key to controlling the activity of **1** and enabled the efficient use of H_2O_2 for the oxidation of alkenes.^[22,23]

The recognition of the role of carboxylic acids and other factors (e.g., solvent composition) in controlling the reactivity of catalyst **1** in the oxidation of alkenes^[23] raises the question as to how conversion of other substrate classes besides alkenes can be controlled and, importantly, how primary and secondary oxidation products can affect the reactivity of the active species formed from **1**, in particular the bis-carboxylato bridged $\text{Mn}^{\text{III,III}}_2$ dimers such as **2** (Figure 1).^[22,23] In this contribution the focus is on the catalytic system employing Mn-tmtacn, carboxylic acids (as co-catalyst) and H_2O_2 (typically 1.05–1.5 equiv.) as terminal oxidant for the selective and atom efficient oxidation of a range of organic substrate classes.

The substrate classes examined in detail are primary and secondary aliphatic and aromatic alcohols, aldehydes, alkenes and alkanes. In all cases, the conditions used for alkene oxidation in our earlier reports^[22] are applied initially, followed by optimisation. The goal, however, was not primarily to identify optimum conditions for each individual substrate but to understand the various factors that affect the reactivity of the Mn-tmtacn catalytic system in each case and to explore which functional groups are oxidised preferentially by the catalytic system. Furthermore, an im-















portant challenge examined is whether compounds containing multiple oxidation sensitive groups can be oxidised selectively without the need of protecting groups. Finally, the tolerance of common protecting groups to the present system is examined.

Results and Discussion

Oxidation of Secondary Alcohols to Ketones

Treatment of aromatic secondary alcohols (Table 1, entries 1–3) by a slow addition of 1.45 equiv. of H_2O_2 in the presence of 0.1 mol% **1** and 1 mol% trichloroacetic acid in acetonitrile afforded the corresponding ketones in excellent conversions and moderate to good isolated yields. Trichloroacetic acid was chosen as co-catalyst since our earlier studies had identified this carboxylic acid to provide the most active catalyst system in general.^[22,23] Side reactions or side products were not observed. Aliphatic secondary alcohols (entries 4–7) were oxidised to the corresponding ketones

Table 1. Oxidation of secondary alcohols to ketones using H_2O_2 catalysed by **1**.^[a]

$\text{R}^1\text{CH}(\text{OH})\text{R}^2 \longrightarrow \text{R}^1\text{C}(=\text{O})\text{R}^2$				
Entry	Substrate	Conversion [%] ^[a]	Product	Isolated yield [%]
1 ^[b]		full		77
2 ^[b]		full		63
3 ^[b]		full		93
4 ^[b]		> 90		31 ^[c]
5 ^[b]		> 95		86
6 ^[b]		full		92
7 ^[b]		full		99

^[a] Conversion was determined by ^1H NMR spectroscopy.

^[b] Reaction conditions: 0.1 mol% **1**, 1.0 mol% $\text{Cl}_3\text{CCO}_2\text{H}$, 1.45 equiv. H_2O_2 , CH_3CN ([substrate] = 1 M), room temperature.

^[c] The isolated yield of cyclohexanone is low, however, this is due to its relatively high volatility (and accompanying loss during work-up) and not due to poor performance of the catalyst.

Table 2. Limitations in the oxidation of secondary alcohols to ketones using H₂O₂ catalysed by **1**.^[a]

$$\text{R}^1\text{CH(OH)R}^2 \longrightarrow \text{R}^1\text{C(=O)R}^2$$

Entry	Substrate	Product(s)	Conversion [%] ^[a]
1 ^[b]		—	< 20
2 ^[b]			> 90 (for both)
3 ^[b]			> 90 (for both)
4 ^[c]			> 95
5 ^[b]		—	< 20
6 ^[b]			12 (for menthol); full (for cyclohexanol)
7 ^[c]		—	< 20

^[a] Conversion was determined by ¹H NMR spectroscopy.

^[b] Reaction conditions: 0.1 mol% **1**, 1.0 mol% Cl₃CCO₂H, 1.45 equiv. H₂O₂, CH₃CN ([substrate] = 1 M), room temperature.

^[c] Reaction conditions: 0.5 mol% **1**, 5.0 mol% Cl₃CCO₂H, 1.45 equiv. H₂O₂, *tert*-BuOH/H₂O (2/1 v/v) ([substrate] = 1 M), room temperature.

in good yields and, importantly, cyclohexanol and cyclooctanol (entries 4 and 5) can be oxidised selectively to cyclohexanone and cyclooctanone, respectively, without formation of Baeyer–Villiger-type oxidation products. This was confirmed by performing the reaction (entry 4) in acetonitrile-*d*₃ followed by direct analysis by ¹H NMR spectroscopy. For longer linear aliphatic alcohols, e.g., 2-octanol (entry 6) and bicyclic alcohols, e.g., isoborneol (entry 7), high conversions and isolated yields were obtained.

Oxidation of several aliphatic secondary alcohols such as 5-nonanol and *L*-menthol (Table 2, entries 1 and 5, respectively) was found not to proceed in acetonitrile under standard reaction conditions. Remarkably, >90% conversion of 5-nonanol to 5-nonanone was obtained when a 1:1 mole ratio mixture of 5-nonanol:cyclohexanol (entry 2) or 5-nonanol:2-octanol (entry 3) was employed. This observation indicates that 5-nonanol is not intrinsically unreactive with respect to the catalyst system but instead a microscopic phase separation of the substrate may be of substan-

tial importance in limiting the reactivity. Indeed, in *tert*-butyl alcohol/H₂O (2/1 v/v), 5-nonanol could be converted to 5-nonanone with greater than 95% conversion (entry 4).

The effect of steric hindrance was inferred in the case of reaction with *L*-menthol and cyclohexanol, which differ in the presence of an isopropyl group adjacent to the hydroxy moiety. In contrast to the case with 5-nonanol, when a 1:1 mixture of cyclohexanol:*L*-menthol was used full conversion of cyclohexanol to cyclohexanone was obtained, however, only 10% conversion of *L*-menthol to menthone was observed (entry 6). Furthermore, in contrast to 5-nonanol, conversion of *L*-menthol was not observed in *tert*-butyl alcohol/H₂O (2/1 v/v) (entry 7).

From these examples it is clear that the current catalyst system is intrinsically unreactive towards certain substrates (e.g., due to steric hindrance). However, for other substrates a simple change in the polarity of the reaction mixture can result in dramatically improved conversions (e.g., by adding another com-

pound which, presumably, interferes with microscopic phase separation or by changing the solvent system).

Oxidation of Primary Alcohols to Carboxylic Acids

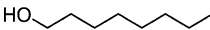
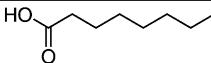
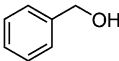
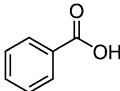
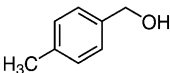
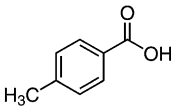
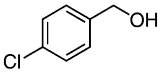
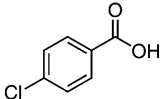
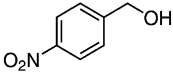
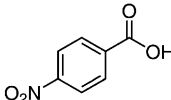
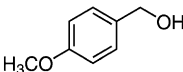
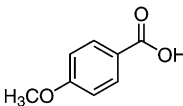
In earlier studies, Mn-tmtacn-based catalysts have been shown to be active in the oxidation of alcohols. Berkessel et al. found that a primary and a secondary alcohol could be oxidised to their corresponding ketone and carboxylic acid when sodium ascorbate was used as additive, albeit with *ca.* 2.5 equiv. of H₂O₂ with respect to substrate.^[17] Zondervan et al. reported the use of Mn-tmtacn for the oxidation of benzyl alcohols to their corresponding aldehydes employing either H₂O₂ or TBHP and to carboxylic acids when excess H₂O₂ (8 equiv. with respect to substrate) was used.^[24] Although acid co-catalysts were not added deliberately in this case, it is nevertheless probable that the activity observed was due to the *in situ* formation of carboxylic acids from the substrates themselves or from decomposition of acetone by H₂O₂ to

form acetic acid.^[25,26] In the present study this aspect is examined further.

Primary aliphatic alcohols, e.g., 1-octanol (Table 3, entry 1), were converted to a mixture of the corresponding aldehyde and carboxylic acid with low to moderate conversion using a range of reaction conditions. This is in agreement with reports that aliphatic alcohols are less reactive than benzylic substrates.^[27] Moreover, selective oxidation of aliphatic alcohols is generally more difficult due to the presence of oxidation sensitive C–H bonds.

Using 0.3 mol% instead of 0.1 mol% of **1** did not lead to improved conversion. As shown in the Supporting Information, Figure S1, the product 1-octanoic acid can displace the carboxylato ligands of the catalyst. In general, complexes of the type [Mn^{III,III}O(RCO₂)₂(tmtacn)₂]²⁺ where R is a linear alkyl group showed lower activity than when trichloroacetato ligands are present.^[23,26] Furthermore, the catalyst loses activity over time due to ligand dissociation and/or reduction to the Mn^{II} oxidation state,^[23] and hence increasing the initial catalyst loading does not result in a significant increase in conversion.

Table 3. Mn-tmtacn-catalysed oxidation of primary alcohols to carboxylic acids using H₂O₂.

$\text{R-CH}_2\text{OH} \longrightarrow \text{R-COOH}$				
Entry	Substrate	Conversion [%] ^[a]	Product	Isolated yield [%]
1 ^[b]		54		37
2 ^[c]		full		> 95
3 ^[d]		full		94
4 ^[d]		full		95
5 ^[e]		91		81
6 ^[e]		< 50		22

^[a] Conversion was determined by ¹H NMR spectroscopy.

^[b] Reaction conditions: 0.4 mol% **1** (stepwise addition), 1.0 mol% Cl₃CCO₂H, 3 equiv. H₂O₂, CH₃CN/H₂O (9/1 v/v) ([substrate] = 1 M), room temperature.

^[c] Reaction conditions: 0.1 mol% **1**, 1.0 mol% Cl₃CCO₂H, 2.05 equiv. H₂O₂, CH₃CN ([substrate] = 1 M), room temperature.

^[d] Reaction conditions: 0.1 mol% **1**, 1.0 mol% salicylic acid, 2.95 equiv. H₂O₂, CH₃CN/H₂O (4/1 v/v) ([substrate] = 0.2 M), room temperature.

^[e] Reaction conditions: 0.4 mol% **1** (stepwise addition), 1.0 mol% salicylic acid, 3 equiv. H₂O₂, CH₃CN/H₂O (4/1 v/v) ([substrate] = 0.2 M), room temperature.

However, adding the catalyst in small portions over time (see the Experimental Section) improved the conversion of 1-octanol to 54% with a 37% yield of the corresponding carboxylic acid (Table 3, entry 1).

The same reaction conditions (0.1 mol% of **1**/1.0 mol% trichloroacetic acid and 3 equiv. H_2O_2) were applied in the oxidation of benzyl alcohol. However, only 60% conversion of benzyl alcohol to a mixture of benzaldehyde and benzoic acid (1:2 ratio) was achieved initially (data not shown). Salicylic acid, 2,6-dichlorobenzoic acid and benzoic acid itself were tested as co-catalyst and all provided full conversion of benzyl alcohol to benzoic acid in excellent isolated yields (96–98%). These results are in contrast to the previous report by Zondervan and co-workers in which benzaldehyde was the sole product obtained.^[24] To investigate this difference further, online monitoring of the oxidation of benzyl alcohol catalysed by **1** and salicylic acid was performed using Raman spectroscopy (Figure 2). Formation of benzaldehyde and benzoic acid as well as the presence of H_2O_2 in the reaction are plotted against time. Over the first hour, the rate of benzaldehyde formation is higher than that of benzoic acid, however, after that period both rates are comparable. The highest yield of benzaldehyde is obtained at 3 h and conversion to benzoic acid occurs eventually. This confirms the observation of oxidation of benzyl alcohol to benzoic acid over 16 h under the present conditions and that selective aldehyde formation was not observed. If the aldehyde is the desired product, performing the reaction with shorter reaction times (such as stopping the reaction within 2 h), followed by separation of the product and

recycling of starting material would be necessary to provide higher overall yields of benzaldehyde.

This system is also efficient in the oxidation of benzyl alcohol derivatives, i.e., 4-methylbenzyl alcohol and 4-chlorobenzyl alcohol (entries 3 and 4, respectively) were converted to their corresponding carboxylic acids in excellent conversions and isolated yields using only 0.1 mol% of **1** and 1.0 mol% of salicylic acid as co-catalyst.

For certain substituted benzyl alcohols a higher catalyst loading was required, i.e., 4-nitrobenzyl alcohol gave 91% conversion and 81% isolated yield of carboxylic acid after applying 0.4 mol% of catalyst in total with stepwise addition of the catalyst (entry 5). However, 4-methoxybenzyl alcohol (entry 6), in particular, gave less than 50% conversion even with higher catalyst loadings. In this case it should be noted that the reaction mixture turned black, which indicates oxidation of the substrate to a redox active quinone-type species that may lead to catalyst decomposition.

Oxidation of Aldehydes to Carboxylic Acids

As expected (*vide supra*) aliphatic aldehydes (Table 4, entries 1–3) were found to be oxidised to the corresponding carboxylic acids in high conversions and good isolated yields. The aromatic aldehydes, benzaldehyde and 4-fluorobenzaldehyde (entries 4 and 5) were converted fully to their corresponding carboxylic acids in 97% and 89% isolated yield, respectively. By contrast, phenylacetaldehyde (entry 6) showed very low conversion and the formation of cleavage products (benzaldehyde and benzoic acid) was observed. Interestingly, the heteroaromatic aldehyde, thiophene-2-carbaldehyde (entry 8), was oxidised to thiophene-2-carboxylic acid as the sole product selectively, with further oxidation^[28] to the corresponding sulfone or sulfone not observed. However, oxidation of furan-2-carbaldehyde did not reach completion even with 0.5 mol% of **1**, with mainly substrate being recovered and only trace amounts of furan-2-carboxylic acid being obtained (entry 9).

Oxidation of Alkenes

Previously, the carboxylic acid-promoted *cis*-dihydroxylation and epoxidation of alkenes catalysed by $[\text{Mn}^{\text{III,III}}_2\text{O}(\text{RCO}_2)_2(\text{tmtacn})_2]^{2+}$ employing H_2O_2 as oxidant was reported by our group.^[22,29,30] This system shows highest activity for electron-rich alkenes, i.e., cyclooctene, cyclohexene, *cis*- and *trans*-heptene, and shows relatively little activity with electron-deficient alkenes such as dimethyl fumarate and dimethyl maleate. A general trend is that the use of the ligand 2,6-

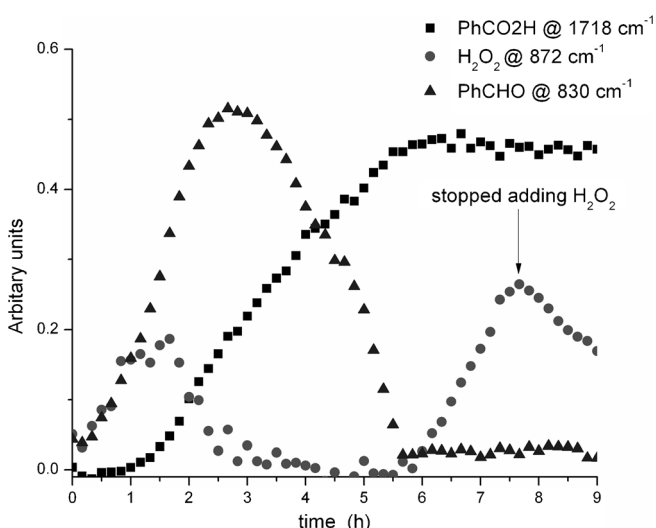
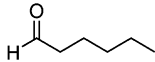
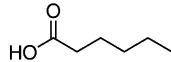
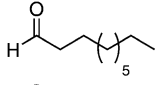
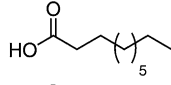
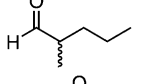
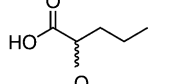
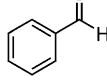
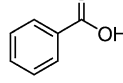
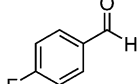
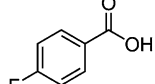
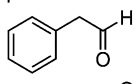
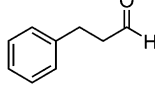
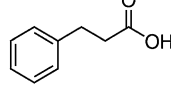
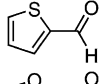
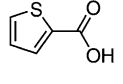
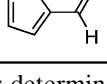


Figure 2. Online monitoring of oxidation of benzyl alcohol (with 3 equiv. of H_2O_2) in CH_3CN catalysed by **1** (0.1 mol%) with salicylic acid (1.0 mol%) under air monitored by Raman spectroscopy ($\lambda_{\text{exc}} = 785 \text{ nm}$).

Table 4. Oxidation of aldehydes to carboxylic acids with H₂O₂ catalysed by **1**.

$\text{R}-\text{C}(=\text{O})\text{H} \longrightarrow \text{R}-\text{C}(=\text{O})\text{OH}$				
Entry	Substrate	Conversion [%] ^[a]	Product	Isolated yield [%]
1 ^[b]		93		61
2 ^[b]		79		56
3 ^[b]		full		66
4 ^[b]		full		97
5 ^[b]		full		89
6 ^[b]		n.d. ^[c]	–	n.d.
7 ^[b]		full		94
8 ^[b]		92		77
9 ^[b]		n.d.	–	n.d.

^[a] Conversion was determined by ¹H NMR spectroscopy.

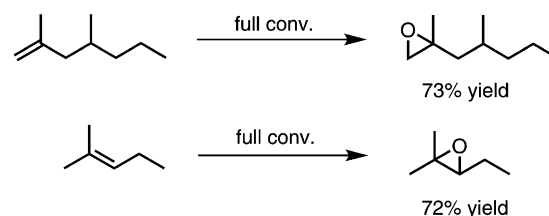
^[b] Reaction conditions: 0.1 mol% **1**, 1.0 mol% Cl₃CCO₂H, 1.45 equiv. H₂O₂, CH₃CN ([substrate] = 1 M), room temperature.

^[c] Not determined (n.d.).

dichlorobenzoic acid leads to higher selectivity towards the *cis*-dihydroxylation products and that the use of salicylic acid leads to higher selectivity for the epoxide products.

To expand the scope of alkene substrates, *gem*-disubstituted and trisubstituted alkenes were examined. For 2,4-dimethyl-1-heptene and 2-methyl-2-pentene, full conversion and good yields (73% and 72%, respectively) of epoxide were obtained employing salicylic acid as co-catalyst and 1.1 equiv. of H₂O₂ (Scheme 1).

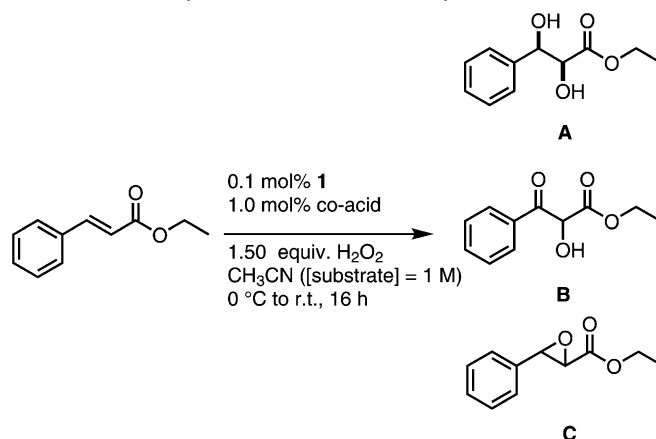
A key question regarding the control of selectivity through the use of various carboxylic acid co-catalysts in the oxidation of less electron-rich alkenes was investigated with ethyl cinnamate, in which the alkene is polarised. A notable difference in selectivity is observed in its oxidation with salicylic acid compared to 2,6-dichlorobenzoic acid as co-catalyst. However, substantial further oxidation of the *cis*-diol product to the corresponding α -hydroxy ketone was observed also (Table 5).



Scheme 1. Oxidation of *gem*-disubstituted and trisubstituted alkenes. Reaction conditions: 0.1 mol% **1**, 1.0 mol% salicylic acid, 1.1 equiv. H₂O₂, 0.5 equiv. 1,2-dichlorobenzene, CD₃CN ([substrate] = 1 M), 0 °C to room temperature.

Oxidation of Alkanes

Although the primary focus of the present study is on oxidative transformations of functional groups, the activity of **1** towards alkane oxidation has been noted previously.^[19a,22] The good to excellent selectivity towards the oxidation of alkenes, alcohols and aldehydes indicates that alkane oxidation is not the preferred mode of action for this catalyst system, however, in the absence of such functional groups activity is

Table 5. Oxidation of ethyl cinnamate with catalyst **1** and various carboxylic acids.


Entry	Co-catalyst	Conversion [%] ^[a]	Product ratio ^[a] A : B : C
1	salicylic acid	full	0.9:1.6:1
2	2,6-dichlorobenzoic acid	60	1.2:0.7:1

^[a] Conversion and product ratio were determined by ¹H NMR spectroscopy.

Table 6. Oxidation of alkanes.

$\text{R}^1\text{---CH}_2\text{---R}^2 \longrightarrow \text{R}^1\text{---C(=O)---R}^2$				
Entry	Substrate	Conversion [%] ^[a]	Product	Isolated yield [%]
1 ^[c]		80		61 ^[b]
2 ^[d]		60		n.d. ^[e]
3 ^[d]		70		37
4 ^[d]		30–40		30
5 ^[d]		70		40
6 ^[d]		70		69

^[a] Conversion of the substrate was determined by Raman spectroscopy ($\lambda_{\text{exc}} = 785 \text{ nm}$) using 1,2-dichlorobenzene as internal standard.

^[b] Yield was determined by ¹H NMR spectroscopy.

^[c] Reaction conditions: 0.1 mol% **1**, 1.0 mol% Cl₃CCO₂H, 4.5 equiv. H₂O₂, CH₃CN ([substrate] = 1 M), 0 °C to room temperature.

^[d] Reaction conditions: 0.1 mol% **1**, 1.0 mol% Cl₃CCO₂H, 1.45 equiv. H₂O₂, CH₃CN ([substrate] = 1 M), 0 °C to room temperature.

^[e] Not determined (n.d.).

Table 7. Oxidation of citronellol under various reaction conditions.

Entry	Co-acid	Equiv. of H ₂ O ₂	Conversion [%] ^[a]	Isolated yield [%]
1	2,6-dichlorobenzoic acid	1.05	50	n.d. ^[b]
2	salicylic acid	1.05	65–80	30
3	salicylic acid	1.15	> 95	62

^[a] Conversion was estimated by ¹H NMR spectroscopy of crude material after work-up.

^[b] Not determined (n.d.).

expected. The activity of **1** with trichloroacetic acid in the selective oxidation of alkanes was examined.

Remarkably, aliphatic cyclic alkanes, such as cyclooctane (Table 6, entry 1), can be converted with good selectivity to the corresponding mono-ketone products. This is attributed to the fact that the system is more active in oxidation of the initially formed alcohol to the corresponding ketone, than towards oxidation of alkanes (*vide supra*).

For aromatic alkanes, the benzylic protons are the most sensitive to oxidation and indeed good conversion and yield of the mono-ketone products could be achieved for several substrates. In the case of ethylbenzene (entry 3), however, the sensitivity of the product to subsequent aldol reactions may have had a substantial impact on the yield obtained. Propylbenzene (entry 4) seems unreactive under the reaction conditions used (trichloroacetic acid as co-catalyst), even increasing the catalyst loading and adjusting the rate of H₂O₂ addition did not improve on the conversion. The system **1**/CCl₃CO₂H showed good selectivity and efficiency for oxidation at the benzylic position in case of indane and tetraline (entries 5 and 6, respectively). Moreover, by controlling the amount of H₂O₂ (1.5 equiv.) added, α -tetralone (the mono-ketone product) can be obtained in high yield (entry 6).

Oxidation of Bifunctional Substrates

A key challenge in modern oxidation catalysis is the selective oxidative transformation of one functional group in the presence of a second oxidation sensitive functional group. As discussed previously, the selectivity of the catalyst, with respect to product formed upon oxidation of an alkene, can be controlled to a significant extent by varying the nature of the carboxylic acid co-catalyst.^[22] Therefore, in a study of functional group selectivity, it is interesting to investigate whether or not the co-catalyst employed exerts similar levels of control.

The bifunctional substrate, citronellol, which contains a trisubstituted electron-rich alkene and a primary alcohol, was oxidised with 1.05 equiv. of H₂O₂ catalysed by **1** together with either 2,6-dichlorobenzoic acid or salicylic acid (Table 7). Good conversion of citronellol (50–80%) to the corresponding epoxy alcohol as the major product was obtained in each case, with salicylic acid providing better conversion. The corresponding diol-, epoxide-, and alkene-aldehyde were also obtained as by-products. With 1.15 equiv. of H₂O₂, >95% conversion of citronellol was achieved and despite the instability of the product during purification (silica gel as stationary phase for column chromatography), the epoxy alcohol could be isolated in 62% yield. Similar preference for epoxidation over alcohol oxidation has been observed before by De Vos et al.^[31] for allyl alcohol and 3-buten-1-ol when using oxalic acid as additive with 2–3 equiv. of H₂O₂.

In the case of 3-vinylbenzaldehyde, where the highly oxidation sensitive aldehyde group is present, the catalysed oxidation was examined with salicylic acid and trichloroacetic acid as co-catalyst (Table 8).

Table 8. Oxidation of 3-vinylbenzaldehyde under various reaction conditions.

Entry	Co-acid	Equiv. of H ₂ O ₂	Product ^[a]
1	salicylic acid	1.50	E
2	salicylic acid	0.80	E
3 ^[b]	salicylic acid	0.80	D
4	CCl ₃ CO ₂ H	1.50	E
5 ^[b]	CCl ₃ CO ₂ H	0.80	D

^[a] Determined by ¹H and ¹³C NMR spectroscopy.

^[b] Reaction was performed under N₂ and in CD₃CN to enable direct analysis by ¹H NMR spectroscopy.

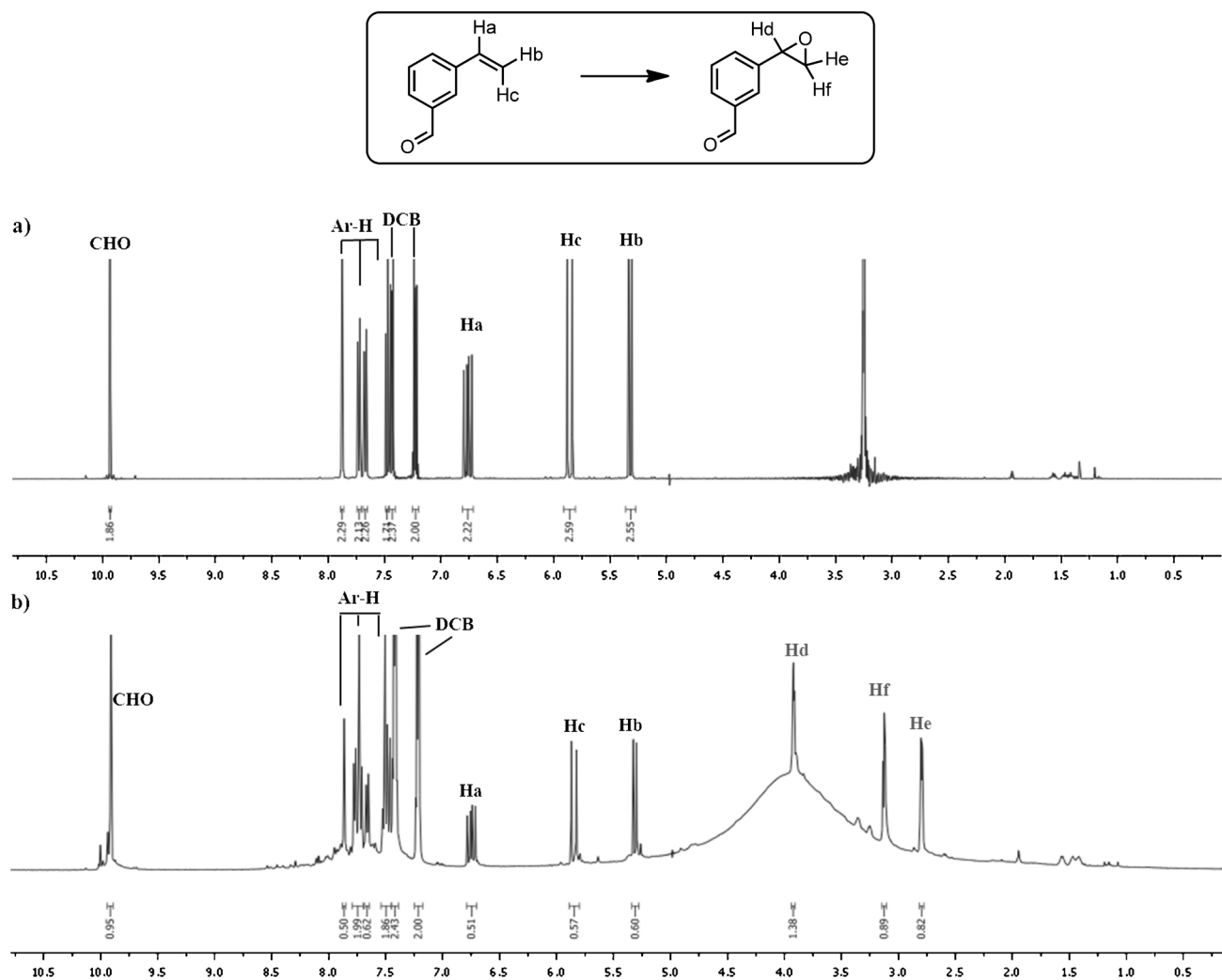


Figure 3. Direct ^1H NMR analysis of oxidation of 3-vinylbenzaldehyde a) at t_0 b) after 7 h in CD_3CN (from Table 8, entry 3).

Conversion and product distribution were confirmed by ^1H NMR spectroscopic analysis after work-up. For both co-catalysts only the epoxide product was obtained with no diol product detected by ^1H NMR spectroscopy. However, almost full conversion of substrate to product bearing both oxidised functional groups (epoxide and carboxylic acid) was obtained even when less than 1 equiv. of H_2O_2 was used (Table 8, entry 2). It was postulated that the oxidation of the aldehyde to the carboxylic acid could occur due to aerobic oxidation during the reaction or work-up and not from the catalytic system itself. To study this in more detail, reactions were performed under a nitrogen atmosphere in acetonitrile- d_3 (degassed) to allow for direct analysis by ^1H NMR spectroscopy (entries 3 and 5, example of analysis is shown in Figure 3). Online monitoring by Raman spectroscopy was also used to follow the conversion of each functional group in real time (for entry 3, see Figure 4 and Figure 5).

Direct ^1H and ^{13}C NMR analyses showed that both reactions from Table 8, entries 3 and 5 provided only epoxy-benzaldehyde as the product. No epoxy-benzoic acid and only trace amounts of diol-benzaldehyde were observed in both cases (see example of ^1H NMR analysis in Figure 3). This means that the alkene moiety of this compound is more reactive than the aldehyde as high selectivity of alkene oxidation was observed with the present system and that the oxidation of the aldehyde unit observed earlier was due to aerobic oxidation during work-up.

To confirm this observation, Raman spectroscopy was used to monitor the reaction online (Table 8, entry 3) by following the intensity of the bands at 1635 cm^{-1} ($\text{C}=\text{C}$ stretching mode) and 1705 cm^{-1} ($\text{C}=\text{O}$ stretching mode) (Figure 4). Plotting the intensity of each band against time shows a lag time lasting the first hour. After that period the intensity of the band due to the alkene moiety decreased rapidly, while the intensity of the band due to the aldehyde did not change substantially (Figure 5). The increase in the

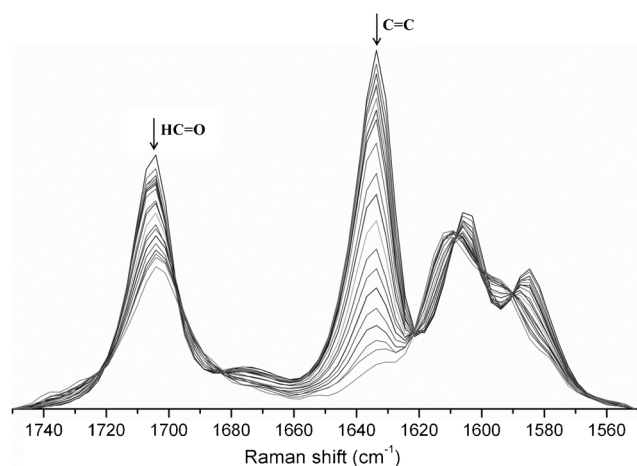


Figure 4. Online reaction monitoring of 3-vinylbenzaldehyde with catalyst **1**, salicylic acid and H_2O_2 under N_2 using Raman spectroscopy ($\lambda_{\text{exc}} = 532 \text{ nm}$).

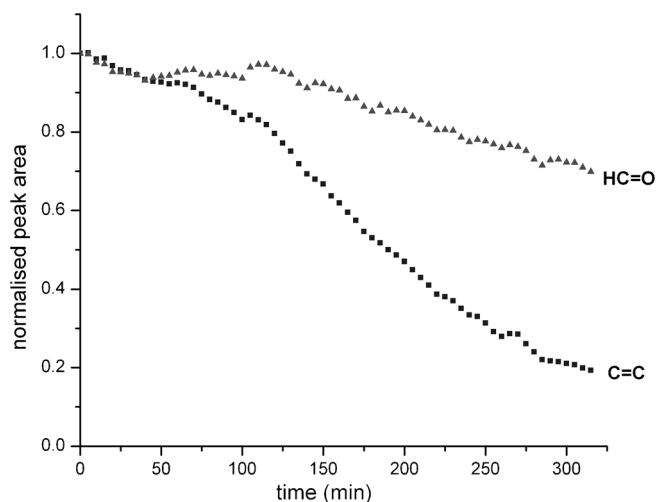
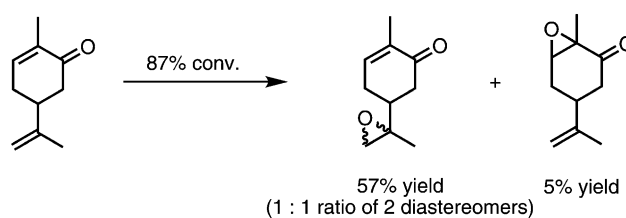


Figure 5. Plot of remaining amount of alkene and aldehyde against time from online monitoring using Raman spectroscopy ($\lambda_{\text{exc}} = 532 \text{ nm}$) of the oxidation of 3-vinylbenzaldehyde with catalyst **1**, salicylic acid and H_2O_2 under N_2 in CD_3CN .

full-width at half maximum of the carbonyl stretching band (at 1635 cm^{-1}) of the aldehyde was due to the steady increase in water content (concomitant with addition of aqueous H_2O_2) (Figure 4). The changes at 1705 cm^{-1} are not due to transformation to the carboxylic acid. These data support the results from ^1H and ^{13}C NMR spectroscopic data (Figure 3).

Oxidation of a substrate containing dissimilar double bonds, i.e., a substrate containing an electron-rich alkene and an electron-deficient alkene in the same molecule, was investigated. When salicylic acid was used as co-catalyst, selectivity for epoxidation of the electron-rich alkene was observed for carvone (Scheme 2). This is in agreement with previous results^[22] that the system is more reactive towards electron-rich alkenes over electron-deficient alkenes, i.e.,



Scheme 2. Oxidation of the diene carvone. Conversion and product yield were determined by ^1H NMR spectroscopy using 1,2-dichlorobenzene (0.5 equiv.) as internal standard. *Reaction conditions:* 0.1 mol% **1**, 1.0 mol% salicylic acid, 1.1 equiv. H_2O_2 , CH_3CN ([substrate] = 1 M), 0°C to room temperature).

the catalyst is electrophilic. For carvone, 57% yield of epoxide from the electron-rich alkene and 5% from electron-deficient alkene were obtained with some side products such as the diepoxide.

Protecting Group Tolerance

The stability of protecting groups under the reaction conditions employed is an important characteristic of the catalyst system. Silyl-based protecting groups, e.g., *tert*-butyldiphenylsilyl (TBDPS) were found to be unstable under the reaction conditions due to the sensitivity of TBDPS groups to H_2O_2 . TBDPS-protected primary aliphatic alcohol and benzyl alcohol were converted to their corresponding aldehyde and carboxylic acid in low yield, and with many by-products from the oxidation of the unprotected alcohol (Table 9, entries 1 and 2 and see also Supporting Information for more details).

The benzyl ether group (Bn) proved to be an unsuitable protecting group with the current catalytic system as well (Table 9, entry 3). Oxidation of benzyl-protected alcohol employing various reaction conditions, i.e., varying the co-acids (trichloroacetic acid, salicylic acid and oxalic acid) and equivalents of H_2O_2 (1.0–3.0 equiv.), gave similar results (by ^1H NMR spectroscopy) with only differences in product ratios. ^1H NMR spectroscopic data demonstrated that not only was the primary alcohol group oxidised to the corresponding aldehyde and carboxylic acid, but also the methylene unit (CH_2) of the benzyl ether group was oxidised. The latter provided the intermediate formation of a hemi-acetal, which is unstable under the reaction conditions employed. Some intermediates were oxidised further to obtain a benzoyl group and some underwent cleavage to afford many undesired products such as pentanol, pentanal, pentanoic acid, benzyl alcohol, benzaldehyde and benzoic acid (see details in the Supporting Information). Their formation was confirmed by GC-MS analysis.

Table 9. Oxidation of protected organic compounds.

Entry	Substrate	Conversion [%] ^[a]	Products	Isolated yield [%]
1 ^[b]		n.d. ^[f]	many products	n.d.
2 ^[b]		n.d.	many products	n.d.
3 ^[c]		n.d.	many products	n.d.
4 ^[d]		80		70
5 ^[e]		75		60
6 ^[e]		80		63
7 ^[e]		full		quant.
8 ^[e]		full		86

^[a] Conversion was determined by ¹H NMR spectroscopy.

^[b] See the Supporting Information, Scheme S1 for reaction conditions and more details.

^[c] See the Supporting Information, Scheme S2 for reaction conditions and more details.

^[d] Reaction conditions: 0.1 mol % **1**, 1.0 mol % salicylic acid, 3 equiv. H₂O₂, CH₃CN/H₂O (4/1 v/v) ([substrate] = 0.2 M), room temperature.

^[e] Reaction conditions: 0.1 mol % **1**, 1.0 mol % salicylic acid, 1.1 equiv. H₂O₂, CH₃CN ([substrate] = 0.5 M), 0 °C to room temperature.

^[f] Not determined (n.d.).

To avoid the cleavage of the protecting group under the reaction conditions used, the benzoyl group (Bz) was used successfully for protecting the alcohol moiety instead (Table 9, entries 4 and 5). The combination of **1** and 1.0 mol % salicylic acid with 3 equiv. H₂O₂ gave 80% conversion of 5-hydroxypentyl benzoate to the corresponding carboxylic acid in 70% (¹H NMR) yield (entry 4). Epoxide products (two diastereomers in a ratio of 1:1) of protected allylic alcohol were obtained in 60% isolated yield (75% conversion; entry 5). Moreover, deprotected substrate or products were not detected by ¹H NMR spectroscopy in either case.

tert-Butoxycarbonyl (Boc)-protected alcohols were found to be stable under these reaction conditions as well. The epoxide product of a Boc-protected allylic alcohol was obtained as the major product (80% con-

version, 63% isolated yield) and minor products were diol and its overoxidation product, α -hydroxy ketone (entry 6). Phthalimide (Phth) is also an alternative protecting group that was found to be suitable with the present system.^[32] A phthalimide-protected allylic aldehyde and an alkene were converted to their corresponding carboxylic acid and epoxide, respectively, both with high conversion and in high isolated yield (entries 7 and 8, respectively). Deprotected species were not observed in either case.

Conclusions

A practical catalytic system employing Mn-tmtacn, with carboxylic acids as co-catalyst and H₂O₂ as terminal oxidant for the oxidation of organic substrates

bearing oxidation sensitive functional groups, i.e., alcohols, aldehydes, alkenes and alkanes, has been described.

The current catalytic system is capable of oxidation of a wide variety of oxidisable groups. For substrates containing more than one oxidation sensitive moiety, selective oxidation of only one functional group could be attained, as exemplified in the selective epoxidation of, e.g., citronellol and 3-vinylbenzaldehyde. The sensitivity of the Mn-tmtacn/carboxylic acid system towards the electronic and steric properties of the substrate can be used to obtain selective oxidation in bifunctional substrates, such as carvone and citronellol. Furthermore, the reactivity of the catalytic system can be fine-tuned by varying, for example, the nature of the carboxylic acid co-catalyst (which are ligands in the bis-carboxylato bridged $\text{Mn}^{\text{III,III}}_2$ dimers **2**) and/or the solvent polarity, thus enabling the oxidation of otherwise challenging substrates. Importantly, the Mn-tmtacn/carboxylic acid system is compatible with substrates bearing a variety of protecting groups such as benzoyl (Bz), *tert*-butoxycarbonyl (Boc) and phthalimide (Phth).

These results open the way to more widespread use of this highly atom-efficient catalyst system, especially on synthetically useful scales.

Experimental Section

See the Supporting Information for experimental details regarding catalysis conditions, synthesis and characterisation of substrates and isolation of products.

General Procedure for Substrate Oxidation

Prior to the experiment, a stock solution containing $[\text{Mn}^{\text{IV}}_2\text{O}_3(\text{tmtacn})_2](\text{PF}_6)_2 \cdot \text{H}_2\text{O}$ (0.03 mol), trichloroacetic acid (0.30 mmol) and H_2O_2 (50 wt% in water, 86 μL) in CH_3CN (10 mL) was prepared at room temperature. The mixture was stirred for 20 min, after which 1.0 mL of this stock solution $\{3.0 \mu\text{mol} [\text{Mn}^{\text{IV}}_2\text{O}_3(\text{tmtacn})_2](\text{PF}_6)_2 \cdot \text{H}_2\text{O}$, 0.1 mol%, 30.0 μmol trichloroacetic acid, 1.0 mol% $\}$ was added to the solution of the substrate (3 mmol) in CH_3CN (2 mL). H_2O_2 (50 wt% in water, typically 1.10–1.45 equiv.) was added *via* syringe pump and the mixture was stirred for 16 h at room temperature. After 16 h, the mixture was added to saturated aqueous NaHCO_3 (20 mL) and CH_2Cl_2 (20 mL). After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried on MgSO_4 and concentrated under vacuum providing the products.

Caution: The drying or concentration of solutions that potentially contain H_2O_2 should be avoided. Prior to drying or concentrating, the presence of H_2O_2 should be tested for, using peroxide test strips, followed by neutralisation on solid NaHSO_3 or another suitable reducing agent. When working with H_2O_2 , especially in acetone, suitable protective safeguards should be in place at all times.

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